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Diastereoselective Synthesis of *trans*-2,3-Dihydrofurans with Pyridinium Ylide Assisted Tandem Reaction

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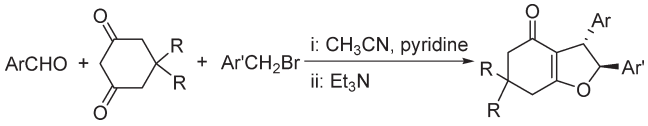

An efficient synthetic procedure for the preparation of fused 2,3-dihydrofuran derivatives was developed with the assistance of pyridinium ylide. A sequential one-pot, two-step tandem reaction starting from pyridine, aromatic aldehyde, dimedone, or 4-hydroxycoumarin and α-phenacyl bromide or *p*-nitrobenzyl bromide with triethylamine as catalyst proceeded smoothly in acetonitrile. ^{1}H NMR spectroscopy and single-crystal analysis demonstrated that the obtained 2,3-dihydrofurans are *trans* isomers.

Introduction

Dihydrofurans belong to an important class of compounds which show a wide range of biological activities and form the basic structure of many natural products.[1,2] The development of new and efficient methods for their synthesis remains an area of current interest, and thus versatile efficient synthetic methods have appeared in the literature.[3] The oxidation coupling reactions of active methylene compounds with alkenes by using transition-metal salts such as manganese(III) acetate[4,5] and cerium(IV) ammonium nitrate[6,7] might be the most common methodology. The reactions of diazo compounds[8] or iodonium ylides[9] with alkenes via organometallic catalysis have also attracted much attention. Another widely utilized method is the so-called "interrupted Feist−Benary reaction", in which the condensation of β-dicarbonyl compounds with α-halo ketones is stopped at the hydroxydihydrofuran stage in the presence of a milder base.[10] Various developments of this

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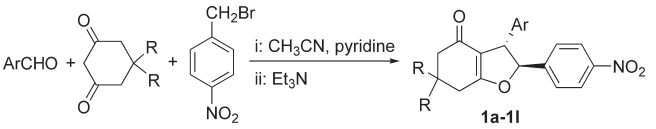
methodology have been reported, and the reaction involves nucleophilic tandem reactions initiated by an attack of stabilized carbanions on suitable electrophiles, followed by a cyclization step,[11−13] in which ylide including sulfonium,[14] phosphonium,[15] arsonium,[16] even ammonium ylides[17] were provided as appropriate reagents. Although a number of methods are available as cited above, the search for newer methods for dihydrofuran synthesis is continuously being pursued. In this paper, we wish to report a new method for the synthesis of 2,3-dihydrofuran derivatives based on a pyridinium ylide assisted three-component tandem reaction.

Results and Discussion

It is important to note that cyclopropane derivatives can be formed in the multicomponent reaction involving aromatic aldehyde, malononitrile, ethyl α-bromoacetate, and pyridine.[18] Chuang and Tsai have reported a reaction involving benzylidene 1,3-dicarbonyl compounds, α-phenacyl bromide, and pyridine for the preparation of 2,3-dihydrofuran derivatives.[19] These interesting results encouraged us to investigate the possibility of tandem reaction with a three-component combination for the efficient synthesis of 2,3-dihydrofurans. In our initial study to assess the utility of *N*-*p*-nitrobenzylpyridinium salt in multicomponent reactions, a mixture of *p*-nitrobenzyl bromide (2.1 mmol), pyridine (5.0 mmol), benzaldehyde (2.0 mmol), and acetylacetone (2.0 mmol) in acetonitrile was refluxed for 2 h, followed by addition of triethylamine (5.0 mmol), and the mixture was stirred overnight. TLC analysis indicated only formation of *N*-*p*-nitrobenzylpyridinium salt, while benzaldehyde and acetoacetone still remained in the solution. This unexpected result indicated that benzaldehyde and acetylacetone could not condensate to give benzylidene acetylacetone under such reaction conditions. The latter is the necessary reagent for further addition reaction of pyridinium ylide. Other 1,3-dicarbonyl compounds such as benzoylacetone, ethyl acetoacetate, and diethyl malonate were also used in the reaction, and it was very disappointing to find that no further reaction occurred. This finding seemed to indicate that pyridine or triethylamine is not basic enough to catalyze the Knoevenagel condensation reaction of benzaldehyde with the above-tested 1,3-dicarbonyl compounds.

TABLE 1. 3,5,6,7-Tetrahedro-2*H*-benzofuran-4-ones from Reactions of *p*-Nitrobenzyl Bromide



1a-1l

entry	compd	Ar	R	yield (%)
1	**1a**	Ph	H	72
2	**1b**	*p*-$CH_3C_6H_4$	H	88
3	**1c**	*p*-$CH_3OC_6H_4$	H	56
4	**1d**	*p*-BrC_6H_4	H	79
5	**1e**	*m*-$NO_2C_6H_4$	H	74
6	**1f**	PhCH=CH	H	87
7	**1g**	Ph	CH_3	74
8	**1h**	*p*-$CH_3C_6H_4$	CH_3	78
9	**1i**	*p*-$CH_3OC_6H_4$	CH_3	61
10	**1j**	*p*-BrC_6H_4	CH_3	77
11	**1k**	*m*-$NO_2C_6H_4$	CH_3	86
12	**1l**	PhCH=CH	CH_3	78

It is well-known that cyclic 1,3-diketones such as 1,3-cyclohexanedione and dimedone are much more reactive than an aliphatic chain 1,3-diketone such as acetylacetone. Thus, we turned our attention to testing the reactivity of 1,3-cyclohexanedione in the above-mentioned three-component reaction. Under similar reaction conditions, the mixture of *p*-nitrobenzyl bromide (2.1 mmol), pyridine (5.0 mmol), benzaldehyde (2.0 mmol), and 1,3-cyclohexanedione (2.0 mmol in acetonitrile was refluxed for 2 h, followed by addition of triethylamine (5.0 mmol), and stirring was continued overnight. We were very satisfied to discover that the fused 2,3-dihydrofuran derivative, 3,5,6,7-tetrahedro-2*H*-benzofuran-4-one **1a**, was obtained in 72% yield (Table 1, entry 1). Similarly, various aromatic aldehydes were tested under the same conditions, and the corresponding 3,5,6,7-tetrahedro-2*H*-benzofuran-4-ones **1b**−**e** were obtained in 56−88% yields (Table 1). This result demonstrated that aromatic aldehydes carrying either electron-donating *p*-methyl and *p*-methoxy or electron-withdrawing *p*-bromo and *m*-nitro groups showed similar reactivity and reacted efficiently to yield the final products. As shown in Table 1, the reaction of cinnamaldehyde also gave phenylvinyl-substituted 3,5,6,7-tetrahedro-2*H*-benzofuran-4-one **1f** in 87% yield (entry 6). Although various solvents such as ethanol, chloroform, toluene, DMF, and even pyridine itself could be used for the reaction, acetonitrile was found to be the most suitable solvent. Then the reactivity of dimedone in the reaction was also screened under similar conditions. A mixture of aromatic aldehyde (2.0 mmol), dimedone (2.0 mmol), *p*-nitrobenzyl bromide (2.1 mmol), and pyridine (5.0 mmol) in acetonitrile (10.0 mL) was refluxed for 2 h, followed by addition of triethylamine (5.0 mmol) and refluxing the mixture overnight. After workup, the expected 6,6-dimethyl-3,5,6,7-tetrahedro-2*H*-benzofuran-4-ones **1g**−**l** were produced in very high yields (Table 1, entries 7−12). These results showed that a one-pot, two-step tandem reaction for the efficient synthesis of

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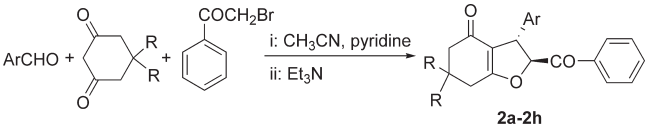
TABLE 2. 3,5,6,7-Tetrahedro-2*H*-benzofuran-4-ones from Reactions of α-Phenacyl Bromide



entry	compd	Ar	R	yield (%)
1	**2a**	Ph	H	66
2	**2b**	*p*-$CH_3C_6H_4$	H	50
3	**2c**	*p*-$CH_3OC_6H_4$	H	47
4	**2d**	*p*-BrC_6H_4	H	46
5	**2e**	Ph	CH_3	63
6	**2f**	*p*-$CH_3C_6H_4$	CH_3	71
7	**2g**	*p*-$CH_3OC_6H_4$	CH_3	71
8	**2h**	*p*-ClC_6H_4	CH_3	75

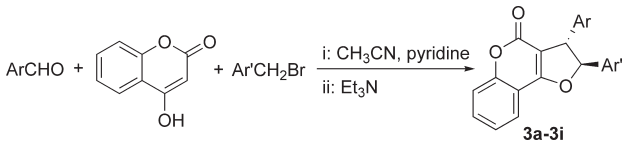
3,5,6,7-tetrahedro-2*H*-benzofuran-4-ones has been successfully established.

The structures of the prepared 3,5,6,7-tetrahedro-2*H*-benzofuran-4-ones **1a**−**l** were fully characterized by ^{1}H and ^{13}C NMR, MS, and IR spectra and elemental analysis. For example, in the ^{1}H NMR spectra of **1a**, the two protons at 2,3-position of dihydrofuran ring display two doublets at 5.61 and 4.25 ppm with the vicinal coupling constant $J = 6.0$ Hz, while in **1c** the two protons at 2,3-position show two doublets at 5.56 and 4.20 ppm with $J = 6.0$ Hz. The similar peak pattern and coupling constant less than 6.0 Hz were also seen in other ^{1}H NMR spectra of prepared 2,3-dihydrofuran derivatives. It has been established that in *cis*-2,3-dihydrofuran the vicinal coupling constant of the two methine protons $J = 7-10$ Hz, while in *trans*-2,3-dihydrofuran vicinal coupling constant $J = 4-7$ Hz.[8−10] According to the careful analysis of ^{1}H NMR data and comparison with the previously reported results, we could tentatively conclude that 2,3-dihydrofuran derivatives **1a**−**l** were the thermodynamicly stable *trans* isomers. The X-ray diffraction determination of single crystals **1f** and **1g** (Supporting Information, Figure S1, S2) further confirmed this conclusion. This interesting result revealed that the pyridinium ylide assisted tandem three-component coupling reaction is highly diastereoselective.

To explore the generality and scope of this tandem reaction, other reactive α-halomethylene compounds such as α-phenacyl bromide were also tested for this reaction, and the results are summarized in Table 2. To our great delight, smooth reactions were observed for all aromatic aldehydes and delivered the final products benzoyl-substituted 3,5,6,7-tetrahedro-2*H*-benzofuran-4-ones **2a**−**h** in good yields (47−75%). The structures of the 3,5,6,7-tetrahedro-2*H*-benzofuran-4-ones **2a**−**h** were also fully established by spectroscopic methods. ^{1}H NMR spectra show only two doublets for two protons at 2,3-position with the coupling constant $J < 6.0$ Hz, which obviously indicated that the 2,3-dihydrofurans **2a**−**h** to be in *trans* configuration as **1a**−**l**. The X-ray analysis of **2a** (Supporting Information, Figure S3) also indicated that the 2-benzoyl and 3-phenyl group existed in the *trans* orientation.

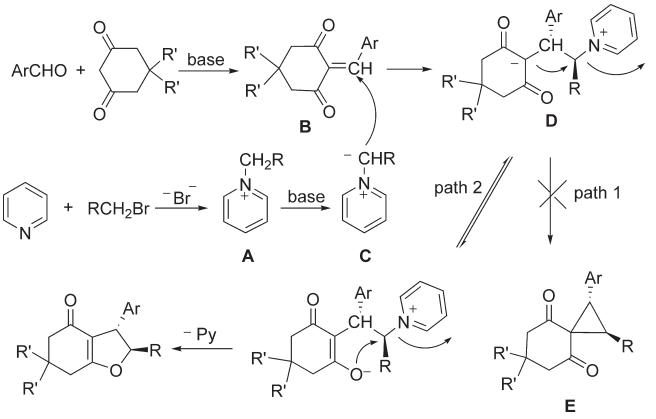
To further demonstrate the potential application of our methodology and to extend the utility of this tandem reaction, the reactivity of another 1,3-dicarbonyl compound,

TABLE 3. 2,3-Dihydrofuro[3,2-*c*]chromen-4-ones from 4-Hydroxycoumarin



entry	compd	Ar	Ar′	yield (%)
1	**3a**	Ph	*p*-$NO_2C_6H_4$	62
2	**3b**	*p*-$CH_3C_6H_4$	*p*-$NO_2C_6H_4$	56
3	**3c**	*p*-$CH_3OC_6H_4$	*p*-$NO_2C_6H_4$	53
4	**3d**	*p*-ClC_6H_4	*p*-$NO_2C_6H_4$	53
5	**3e**	Ph	PhCO	75
6	**3f**	*p*-$CH_3C_6H_4$	PhCO	81
7	**3g**	*p*-$CH_3OC_6H_4$	PhCO	62
8	**3h**	*p*-ClC_6H_4	PhCO	68
9	**3i**	*m*-$NO_2C_6H_4$	PhCO	50

SCHEME 1. Proposed Formation Mechanism of 2,3-Dihydrofuran Derivatives



4-hydroxycoumarin, was also explored. When 4-hydroxycoumarin was treated with aromatic aldehydes, pyridinium salts formed in situ from *p*-nitrobenzyl bromide, or α-phenacyl bromide under similar conditions, the expected 2,3-dihydrofuro[3,2-*c*]chromen-4-ones **3a**−**i** were obtained in 50−81% yields (Table 3). 2,3-Dihydrofuro[3,2-*c*]chromen-4-ones have been widely found in nature and reported to have various biological activities.[20] The structures of **3a**−**i** were clearly assigned as *trans* isomers by the analysis of the vicinal coupling constant of the two methine protons and further confirmed by the X-ray analysis of **3e** (Supporting Information, Figure S4).

This tandem reaction proceed very straightforwardly, although the exact mechanism of this reaction is not very clear. To explain the mechanism of this one-pot multicomponent reaction, we propose a plausible reaction course, which is illustrated in Scheme 1. The first step is the formation of the two reaction intermediates. *N*-*p*-Nitrobenzylpyridinium bromide (**A**) was produced from the addition of *p*-nitrobenzyl bromide to pyridine, and the 2-arylidene-1,3-cyclohexanedione (**B**) was formed by the Knoevenagel

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condensation of the respective aromatic aldehyde with 1,3-cyclohexanedione catalyzed by pyridine. The second step is a Michael addition of a pyridinium ylide (**C**) which is formed by deprotonation of the *N*-*p*-nitrobenzylpyridinium species (**A**) by triethylamine to (**B**) to afford the zwitterion salt (**D**). On heating, this zwitterion salt might react further according to two different paths to give two different products. In the first path, the intramolecular substitution of the carbanion replaces pyridine with formation of the cyclopropane **E**, which is not observed here. In the second path, the carbanion transfers to resonance-stabilized enolate through the keto−enol tautomerism, which in turn substitutes pyridine to give the final product 2,3-dihydrofuran. The last step is a typical intramolecular S_N2 substitution reaction. The stereochemistry of the S_N2 reaction requires nucleophilic enolate attack from the back side of the electrophilic carbon atom bearing the leaving pyridyl group, which subsequently assumes two steric larger 2-*p*-nitrophenyl group and 3-aryl groups in a stereochemical opposite position for the sake of stereohindance in the carbanion (**D**) and in the transition state. Thus, only *trans* isomeric 2,3-dihydrofuran was produced after cyclization. In this proposed reaction mechanism pyridine plays very important role. It acts as a nucleophilic tertiary amine to form pyridinium cation and zwitterionic salt, as a base to catalyze Knoevenagel condensation, and as a good leaving group to finish the intramolecular substitution reaction.

Conclusions

A novel tandem three-component coupling reaction leading to selective and high-yielding fused 2,3-dihydrofuran derivatives is developed from readily avaible starting materials. The reaction proceeds via Michael addition and intramolecular cyclization of pyridinium ylide formed in situ under very convenient conditions. This protocol can provide a novel and effective methodology for the preparation of 2,3-dihydrofurans in a stereoselective fashion. A proposed mechanism for this diastereoselective formation of *trans*-2,3-dihydrofuran derivatives were suggested on the basis of steric hindnace in the cyclization step. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

Experimental Section

Typical Procedure for the Preparation of 2-(*p*-Nitrophenyl)-3-phenyl-3,5,6,7-tetrahedro-2*H*-benzofuran-4-one (Entry 1, Table 1). A mixture of benzaldehyde (2.0 mmol), 1,3-cyclohexanedione (2.0 mmol), *p*-nitrobenzyl bromide (2.1 mmol), and pyridine (5.0 mmol) in acetonitrile (10 mL) was refluxed for 2 h. Subsequently, triethylamine (5.0 mmol) was added to the solution. The resulting mixture was refluxed for12 h. After completion of the reaction was checked by TLC, the solvent was evaporated in a rotatory evaporator and the crude product was washed with water and filtered off. Recrystallization from ethanol gave pure product **1a**: white solid; yield 72%; mp 156 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, J = 8.4 Hz, 2H, *p*-$NO_2C_6H_4$), 7.44 (d, J = 8.4 Hz, 2H, *p*-$NO_2C_6H_4$), 7.36 (t, J = 7.2 Hz, 2H, C_6H_5), 7.29 (t, J = 7.2 Hz, 1H, C_6H_5), 7.21 (d, J = 7.2 Hz, 2H, C_6H_5), 5.61 (d, J = 6.0 Hz, 1H, CH), 4.25 (d, J = 6.0 Hz, 1H, CH), 2.78−2.66 (m, 2H, CH_2), 2.45−2.35 (m, 2H, CH_2), 2.22−2.17 (m, 2H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.4, 176.8, 147.8, 147.3, 141.3, 129.1, 127.5, 127.1, 126.0, 124.2, 115.9, 92.7, 54.6, 36.9, 24.0, 21.8; MS(ESI-) m/z = 334.82; IR (KBr disk) 3444(w), 2896(w), 1641(vs), 1602(m), 1517(s), 1454(m), 1392(s), 1350(s), 1255(m), 1224(w), 1175(m), 1144(w), 1109(w), 1066(m), 1027(w), 978(m), 947(w), 836(m), 759(m), 703(m) cm^{-1}. Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.46; H, 5.40; N, 3.82.

Typical Procedure for the Preparation of 2-Benzoyl-3-phenyl-3,5,6,7-tetrahedro-2*H*-benzofuran-4-one (Entry 1, Table 2). A mixture of benzaldehyde (2.0 mmol), 1,3-cyclohexanedione (2.0 mmol), phenacyl bromide (2.1 mmol), and pyridine (5.0 mmol) in acetonitrile (10 mL) was refluxed for 2 h. Subsequently, triethylamine (5.0 mmol) was added to the solution. The resulting mixture was refluxed for 12 h. Recrystallization from ethanol gave pure product **2a**: white solid; yield 66%; mp 128−130 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, J = 7.2 Hz, 2H, C_6H_5), 7.62 (t, J = 7.8 Hz, 1H, C_6H_5), 7.46 (t, J = 7.8 Hz, 2H, C_6H_5), 7.35 (t, J = 7.2 Hz, 2H, C_6H_5), 7.29 (t, J = 7.2 Hz, 1H, C_6H_5), 7.24 (d, J = 7.2 Hz, 2H, C_6H_5), 5.87 (d, J = 4.8 Hz, 1H, CH), 4.42 (d, J = 4.8 Hz, 1H, CH), 2.76−2.68 (m, 2H, CH_2), 2.34−2.32 (m, 2H, CH_2), 2.17−2.09 (m, 2H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.2, 192.9, 177.3, 141.2, 134.2, 133.3, 129.03, 128.98, 128.9, 127.6, 127.3, 116.5, 91.6, 48.9, 36.8, 23.9, 21.7; MS(ESI-) m/z = 317.64; IR (KBr disk) 3443(w), 3058(w), 2974(w), 1701(s), 1639(vs), 1493(w), 1450(m), 1394(s), 1228(s), 1178(s), 1108(m), 1061(m), 1022(m), 961(s), 873(m), 777(m), 698(s) cm^{-1}. Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70. Found: C, 79.50; H, 5.93.

Typical Procedure for the Preparation 2-(*p*-Nitrophenyl)-3-phenyl-2,3-dihydrofuro[3,2-*c*]chromen-4-one (Entry 1, Table 3). A mixture of benzaldehyde (1.0 mmol), 4-hydroxycoumarin (1.0 mmol), *p*-nitrobenzyl bromide (1.05 mmol), and pyridine (3.0 mmol) in acetonitrile (10 mL) was refluxed for 2 h. Subsequently, triethylamine (3.0 mmol) was added to the solution. The resulting mixture was refluxed for 12 h. Recrystallization from ethanol gave pure product **3a**: white solid; yield 62%; mp 186−188 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, J = 7.8 Hz, 2H, *p*-$NO_2C_6H_4$), 7.85 (d, J = 7.8 Hz, 1H, C_6H_4), 7.66 (t, J = 7.8 Hz, 1H, C_6H_4), 7.52 (d, J = 8.4 Hz, 2H, *p*-$NO_2C_6H_4$), 7.45 (d, J = 8.4 Hz, 1H, C_6H_4), 7.41−7.38 (m, 3H, C_6H_4, C_6H_5), 7.34 (t, J = 7.2 Hz, 1H, C_6H_5), 7.28 (d, J = 7.2 Hz, 2H, C_6H_5), 5.95 (d, J = 6.0 Hz, 1H, CH), 4.56 (d, J = 6.0 Hz, 1H, CH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 159.3, 155.5, 148.2, 146.3, 139.5, 133.2, 129.4, 128.2, 127.4, 126.2, 124.4, 124.3, 123.0, 117.3, 112.1, 104.7, 94.3, 55.4; MS(ESI-) m/z = 384.50; IR (KBr disk) 3434(w), 3073(w), 2922(w), 1723(vs), 1647(s), 1603(m), 1515(s), 1452(w), 1405(m), 1345(s), 1272(w), 1223(w), 1190(w), 1156(w), 1098(m), 1037(m), 970(w), 920(m), 853(w), 764(m) cm^{-1}. Anal. Calcd for $C_{23}H_{15}NO_5$: C, 71.68; H, 3.92; N, 3.63. Found: C, 71.54; H, 4.27; N, 3.20.

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Supporting Information Available: Experimental details and characterization data including IR, MS, and ^{1}H and ^{13}C NMR spectra as well as X-ray crystallography for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.